Abstract

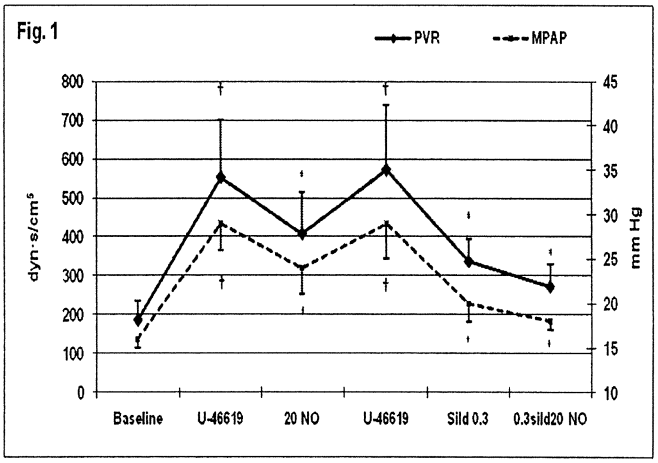
Title: Effect of intravenous sildenafil on right and left ventricular function in pigs.

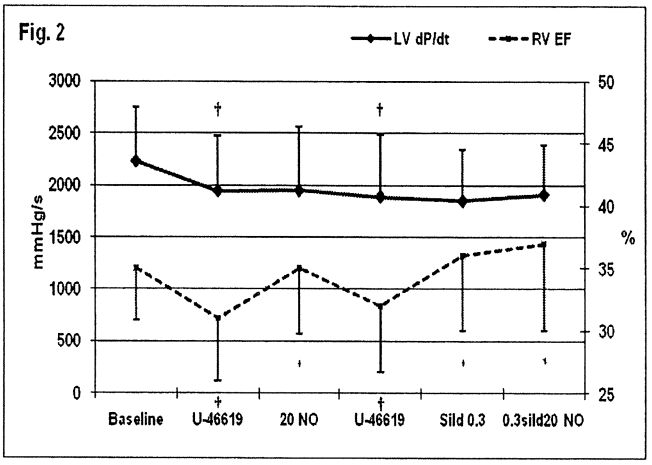
Author(s): G. Diet, L. Foubert*, Y. Taeymans, G. Van Nooten, Y. Van Belleghem, D. De Wolf, E. Mortier, P. Wouters

Hospital/Institute: University Hospital, Ghent - OLV Hospital, Aalst*

Introduction : Sildenafil, a phosphodiesterase 5 inhibitor, is widely used in the treatment of paediatric patients with pulmonary hypertension (PHT) from different origins (1). It increases the bioavailability of cGMP and supports endogenous pulmonary vasodilatation (2). Therefore, intravenous (IV) sildenafil may be an attractive alternative for inhaled NO (iNO) in acute PHT. However, the effect of cGMP on myocardial contractility is controversial. It can theoretically exert positive and negative inotropic effects via different mechanisms (3). We investigated the effect of IV sildenafil on systemic and pulmonary haemodynamics, as well as on right ventricular (RV) function and left ventricular (LV) contractility in an animal model of PHT.

Materials and Methods : In a first group of 8 anaesthetized open-chest pigs, we investigated the haemodynamic effect of 0.25 mg/kg, 0.50 mg/kg and 1.00 mg/kg IV sildenafil. Then we induced PHT in the next group of 8 pigs, with a stable thromboxane analogue U-46619. In this group we assessed the effect of 20 ppm iNO, 0.30 mg/kg sildenafil IV, and a combination of both. Right ventricular ejection fraction (RVEF) was used to evaluate RV function, whereas LV dP/dt max was used to assess LV contractility. ANOVA with appropriate post hoc testing (group I) and paired T-test (group II) were used for statistical analysis.





† $p < 0.05$ vs Baseline, * $p < 0.05$ vs U-46619

Results: In group I, no statistically significant changes in LV dP/dt max, mean arterial pressure and cardiac output (CO) were observed: 1611±279 at a cumulative sildenafil dose of 1.75 mg/kg vs 1796±295 mm Hg/s at baseline, 57±10 vs 61±9 mm Hg and 3.3±0.6 vs 3.6±0.4 L/min, respectively. Mean pulmonary arterial pressure (MPAP) decreased (13±2 vs 15±2 mm Hg, $p<0.01$) and RVEF increased (40±9 vs 35±6 %, $p<0.01$). In group II, iNO, sildenafil (sild) and the combination of both decreased MPAP and pulmonary vascular resistance (PVR) significantly vs values with U-46619 (fig.1). Both iNO and sildenafil alone reduced the pulmonary vascular resistance /systemic vacular resistance ratio to a similar extent (24.9±5.7 and 23.0±5.2 vs 35.1±4.7). The combination of both almost restored this ratio to baseline values prior to the induced PHT (18.0±4.0 vs 14.1±1.7), without significant effects on LV dP/dt max. Sildenafil induced a more pronounced pulmonary vasodilatation than iNO, with a statistically significant but clinically acceptable decrease in mean arterial pressure (63±9 vs 69±9 mm Hg, $p<0.05$). Fig. 2 illustrates that neither iNO nor sildenafil altered LV dP/dt max. They both increased RVEF significantly. Sildenafil alone was able to restore RVEF to a level almost identical to the one before infusion of U-46619, without changes in CO (3.1±0.5 vs 3.1±0.6 L/min,NS).

Discussion: In an animal model of acute PHT, intravenous administration of 0.30 mg/kg sildenafil caused powerful pulmonary vasodilatation with clinically acceptable effects on the systemic circulation. It improved right ventricular function significantly and had no effect on LV myocardial contractility. The combination of sildenafil with iNO resulted in an additional pulmonary vasodilatation, without further effects on the systemic circulation, nor on right and left ventricular function.

Conclusion: This animal study suggests that IV sildenafil may be an alternative for iNO in the treatment of acute PHT.

References: **1**. Huddleston A.J. et al. Pediatr Cardiol. 2009. 30.7:871-82. **2**. Shekerdemian L.S. et al. Pediatr Res. 2004. 55:413-18. **3**. Vandecasteele G. et al. J Physiol. 2001. 533.2:329-40.